[Billing Code 4140-01-P]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Government-Owned Inventions; Availability for Licensing

AGENCY: National Institutes of Health, Public Health Service, HHS

ACTION: Notice

SUMMARY: The inventions listed below are owned by an agency of the U.S. Government and are available for licensing in the U.S. in accordance with 35 U.S.C. 207 to achieve expeditious commercialization of results of federally-funded research and development. Foreign patent applications are filed on selected inventions to extend market coverage for companies and may also be available for licensing.

ADDRESS: Licensing information and copies of the U.S. patent applications listed below may be obtained by writing to the indicated licensing contact at the Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852-3804; telephone: 301-496-7057; fax: 301-402-0220. A signed Confidential Disclosure Agreement will be required to receive copies of the patent applications.

Lenalidomide Analogs for the Treatment of Neurodegenerative Disorders and Cancer

Description of Technology: Inflammatory processes associated with the over-production of tumor necrosis-alpha (TNF-α), a potent activator of the immune system accompany numerous neurodegenerative diseases. TNF-α has been validated as a drug target with the development of the inhibitors Enbrel and Remicade (fusion antibodies) as prescription medications. Both, however, are large macromolecules that require direct injection and have limited brain access. The classical drug, thalidomide is being increasingly used in the clinical management of a wide spectrum of immunologically-mediated and infectious diseases, and cancers. The NIA inventors developed and assessed novel thio analogs of lenalidomide (Celegene's Revlimid and an analog of thalidomide) as immunomodulatory agents, with the potential to reduce chronic systemic and central nervous system inflammation. These compounds were synthesized and evaluated for their TNF-α inhibitory activity. This invention was extended from the inventors' prior work to develop potent compounds to reduce neuroinflammation as a treatment strategy for neurodegenerative disorders. The current studies focus the compounds activity in classical models of neurodegeneration as well as cancer.

Potential Commercial Applications:

• Treatment for blood disorders (myelodysplastic syndrome), cancer (multiple myeloma), inflammatory processes and erythema

• Immunomodulatory agents

• Reduce chronic systemic and central nervous system inflammation

Competitive Advantages:

• Effective smaller molecular weight compound that can enter brain among current agents

• Experimental therapeutic to reduce inflammation systematically and within the brain

• Effective in reducing proinflammatory cytokines than existing agents

Development Stage:

• Prototype

• Clinical

• In vitro data available

• In vivo data available (animal)

Inventors: Nigel H. Greig, Weiming Luo, David Tweedie, Harold W. Holloway, Qian-sheng Yu (all of NIA)

Publication: Luo W, et al. Design, synthesis and biological assessment of novel N-substituted 3-(phthalimidin-2-yl)-2,6-dioxopiperidines and 3-substituted 2,6-dioxopiperidines for TNF-alpha inhibitory activity. Bioorg Med Chem. 2011 Jul 1;19(13):3965-3972. [PMID 21658960]

Intellectual Property: HHS Reference No. E-045-2012/0 — U.S. Patent Application No. 13/310,242 filed 02 Dec 2011

Related Technologies: HHS Reference No. E-189-2003/0 —

• U.S. Patent No. 7,973,057 issued 05 Jul 2011

• U.S. Application No. 13/153,355 filed 03 Jun 2011

• and related international patents/patent applications

Licensing Contact: Whitney Hastings, Ph.D.; 301-451-7337; hastingw@mail.nih.gov

Use of Englerin A, a Small Molecule HSF1 Activator, for the Treatment of Diabetes, Obesity, and Other Diseases Associated with Insulin Resistance

Description of Technology: Insulin resistance is a causative factor for type 2 diabetes, obesity and a number of other conditions. This technology claims methods for treating diseases or conditions associated with insulin resistance using the small molecule epoxy-guaiane derivative englerin A and related compounds. The compounds are claimed separately in a related NIH technology.

The inventors have shown that englerin A, a compound originally isolated from the Phyllanthus plant and previously identified as an anti-cancer agent, can also be used to treat insulin resistance. Insulin resistance is associated with reduced gene expression and production of heat shock protein 70 (HSP70). Using a mouse with tumor model, the inventors discovered that administration of englerin A decreases blood glucose levels by activating transcription of HSF1, thereby increasing the expression and secretion of HSP70. Thus, englerin A and related compounds represent potential drugs for the treatment of a variety of conditions associated with insulin resistance.

Potential Commercial Applications: Treatment of diseases or conditions associated with insulin resistance, such as type 2 diabetes, obesity, inflammation, metabolic syndrome, polycystic ovary disease, arteriosclerosis, non-alcoholic fatty liver disease, reproductive abnormality of a female, and growth abnormality.

Competitive Advantages: Use of small-molecule compounds targeting HSF1 represents a novel approach to the treatment of type 2 diabetes and other conditions caused by insulin resistance.

Development Stage:

• In vitro data available

• In vivo data available (animal)

Inventors: Leonard Neckers et al. (NCI)

Publication: Ratnayake R, et al. Englerin A, a selective inhibitor of renal cancer cell growth, from Phyllanthus engleri. Org Lett. 2009 Jan 1;11(1):57-60. [PMID 19061394]

Intellectual Property: HHS Reference No. E-042-2012/0 — U.S. Application No. 61/584,526 filed 09 Jan 2012

Related Technologies: HHS Reference No. E-064-2008/2 — U.S. Application No. 12/811,245 filed 29 Jul 2010 and related international applications

Licensing Contact: Tara Kirby, Ph.D.; 301-435-4426; tarak@mail.nih.gov

Collaborative Research Opportunity: The NCI Urologic Oncology Branch is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize epoxyguaianes as anti-type 2 diabetes agents. For collaboration opportunities, please contact John Hewes, Ph.D. at hewesj@mail.nih.gov.

A Novel, Non-invasive Test for the Detection of Chromaffin Cell Tumors Associated with SDHB Mutation

Description of Technology: Pheochromocytomas/ paragangliomas (PHEOs/PGLs) are hormone producing tumors of the sympathetic nervous system located in the adrenal glands (which sit atop the kidneys) or the paraganglia, which are distributed throughout the upper body. Mutations in the gene of a mitochondrial protein, succinate dehydrogenase B (SDHB), can cause PHEOs/PGLs that have a high rate of malignancy. Normally, PHEOs/PGLs can be diagnosed by measuring increased stress hormone metabolites in blood or urine. However, detection of *SDHB*-related PHEOs/PGLs can be difficult as up to ten percent do not show elevated stress hormone metabolites, and thus proper diagnosis requires expensive and often not-widely-available imaging. In addition, *SDHB*-PHEO/PGL patients need regular imaging to rule out development of metastases and family members of patients with *SDHB*-PHEOs/PGLs need genetic testing for risk evaluation. A significant need remains for additional diagnostic methods to prevent misdiagnosis of patients with non-secreting or metastatic *SDHB*-PHEOs/PGLs and risk evaluation of family members.

Researchers at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) have developed methods to identify *SDHB* mutation based on the presence/ absence of just four urinary peptides. Further data from the researchers suggests that metastatic PGLs can also be identified in patients based on their urinary peptide pattern.

Potential Commercial Applications: Diagnostic kits for non-secreting or metastatic PHEOs/PGLs in patients, or for risk assessment of their family members.

Competitive Advantages:

• Cost-effective

• Non-invasive

• Sample collection could occur at home or doctor's office

Inventors: Karel Pacak (NICHD) et al.

Intellectual Property: HHS Reference No. E-201-2011/0 — U.S. Provisional Application No. 61/498,428 filed 17 Jun 2011

Licensing Contact: Patrick P. McCue, Ph.D.; 301-435-5560; mccuepat@mail.nih.gov

Collaborative Research Opportunity: The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate or commercialize a urine-based diagnostic to detect proteins associated with pheochromocytoma/paraganglioma (PHEO/PGL). For collaboration opportunities, please contact Joseph M. Conrad III, Ph.D., J.D. at jmconrad@mail.nih.gov.

T Lymphocyte (T cell) Clones that Recognize the Tumor Associated Antigens gp100 and MART-1

Description of Technology: Scientists at the National Institutes of Health (NIH) have developed cytotoxic, CD8+ T lymphocyte (T cell) clones, designated R6C12 and JKF6, derived from tumor infiltrating lymphocytes (TIL) of cancer patients. The R6C12 clone recognizes the tumor associated antigen (TAA) gp100 and has been shown to be specific for amino acids 209-217 of the gp100 protein, known as the 210M or g209-2M peptide. The JKF6 clone recognizes the TAA MART-1, specifically the peptide

represented by amino acids 27-35 of the MART-1 protein. TIL are a subset of T cells found within tumors that have high specificity for the antigen(s) expressed by that tumor.

MART-1 (also known as Melan-A) and gp100 are TAAs expressed primarily by melanomas and at low levels in normal melanocytes. MART-1 is a melanocyte differentiation antigen found on the surface of these cells and gp100 is a transmembrane glycoprotein. Both proteins are located in the melanosomes of normal melanocytes, the melanin producing organelle of these cells. In cancer patients with gp100+ and or MART-1+ tumors, T cells, such as TIL, have been identified that recognize particular epitopes of these TAAs to mediate tumor cell killing. Cancer vaccines and adoptive T cell immunotherapies have been developed to generate immune responses to target one or both of these antigens for cancer regression.

Potential Commercial Applications:

• Characterize and develop T cell receptors for use in adoptive immunotherapy of MART-1+ and gp100+ cancers

• Develop molecular screens to characterize tumor antigen expression of patient samples and/or laboratory cell lines

• Develop research materials to better understand T cell functions, including antigen recognition, cell signaling, and immune responses

• Positive controls for T cells with high reactivity to gp100 and MART-1

Competitive Advantages:

• These T cell clones were isolated and selected from the bulk TIL cultures of the respective patients from which they were derived due to their superior reactivity to their TAA antigen.

• Significant data has been collected on their characteristics, including identification of the tumor associated antigen and specific cancer peptide recognized by the T cell receptor of each clone.

Development Stage:

• Pre-clinical

• Clinical

• In vitro data available

• In vivo data available (human)

Inventors: Mark E. Dudley and Steven A. Rosenberg (both of NCI)

Publications:

1. Dudley M, et al. Cancer regression and autoimmunity in patients after clonal repopulation with antitumor lymphocytes. Science. 2002 Oct 25;298(5594):850-854. [PMID 12242449]

2. Dudley M, et al. Adoptive transfer of cloned melanoma-reactive T lymphocytes for the treatment of patients with metastatic melanoma. J Immunother. 2001 Jul-Aug;24(4):363-373. [PMID 11565838]

Intellectual Property: HHS Reference No. E-267-2010/0 — Research Tool. Patent protection is not being pursued for this technology.

Related Technologies:

• HHS Reference No. E-057-1994 — Melanoma Antigens and Their Use in Diagnostic and Therapeutic Methods

• HHS Reference No. E-086-2001 — Peptides of a Melanoma Antigen and Their Use in Diagnostic, Prophylactic, and Therapeutic Methods

• HHS Reference No. E-106-2004 — Compositions Comprising T cell Receptors and Methods of Use Thereof

• HHS Reference No. E-304-2006 — Modified T cell Receptors and Related Materials and Methods

• HHS Reference No. E-059-2007 — gp100-specific T cell Receptors and Related Materials and Methods

• HHS Reference No. E-312-2007 — Modified T cell Receptors and Related Materials and Methods

• HHS Reference No. E-257-2008 — Melanoma Associated Peptide Analogues and Vaccines Against Melanoma

• HHS Reference No. E-261-2008 — Melanoma Associated Antigenic Polypeptide, Epitopes Thereof and Vaccines Against Melanoma

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Date

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